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EXAMINER	
KWON, BRIAN YONG S	

ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/615,703	BENKOVIC ET AL.	
	Examiner	Art Unit	
	Brian-Yong S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *52-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. Acknowledgement is made of applicants' filing of the instant application as a Request for Continued Examination (RCE) under 37 CFR 1.1114.

2. The examiner for the instant application has changed. The current examiner assigned to this application is Brian-Yong S. Kwon. Claims 52-61 are presented for examination.

3. Acknowledgement is made of applicant's amendment/remarks filed on 12/29/2008. By the amendment, claims 1, 2, 12-14 and 45-50 have been cancelled and claims 52-61 have been newly added.

4. Applicant's arguments have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of actions being applied to the instant application.

Priority

5. Acknowledge is made of applicant's amendment to the specification filed on 12/19/2008. Applicant is claiming benefit of earlier filing date and cross-references to other applications. However, the domestic claim filed on 12/19/08 was not entered because the domestic priority claim was not filed during the time period set forth in 37 CFR 1.78(a). For original applications filed under 35 U.S.C. 111(a) (other than a design application) on or after November 29, 2000, the time period is during the pendency of the

application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior-filed provisional application. If the reference required by 35 U.S.C. 119(e) and paragraph (a)(5) of this section is presented in a nonprovisional application after the time period provided by paragraph (a)(5)(ii) of this section, the claim under 35 U.S.C. 119(e) for the benefit of a prior-filed provisional application may be accepted during the pendency of the later-filed application if the reference identifying the prior-filed application by provisional application number was unintentionally delayed. A petition to accept an unintentionally delayed claim under 35 U.S.C. 119(e) for the benefit of a prior-filed provisional application must be accompanied by: (i)

The reference required by 35 U.S.C. 119(e) and paragraph (a)(5) of this section to the prior-filed provisional application, unless previously submitted; (ii) The surcharge set forth in § 1.17(t); and (iii) A statement that the entire delay between the date the claim was due under paragraph (a)(5)(ii) of this section and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 52-61 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating the specific condition of DNA methyltransferase mediate, bacterium induced disease (i.e., otitis media) with the

administration of said boron containing compound, does not reasonably provide enablement for "treating DNA methyltransferase mediate, bacterium induced disease" with the administration of said compond. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The instant invention relates to a method of treating DNA methyltransferase mediate, bacterium induced disease comprising administering a compound of said formula recited in claim 52.

There are no known compounds of similar structure which have been demonstrated to treat all disease conditions mediated by DNA methyltransferase. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits.

The relative skill of those in the pharmaceutical art is high. The unpredictability of the pharmaceutical art is very high. As stated above, applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The claims are very broad. The scope of the instant claims encompasses treatment of multiple complex disorders that may have unrelated manifestations such as various bacterial, fungal or viral diseases including actinomycosis, anthrax, bacterial dysentery, botulism, brucellosis, cellulitis, cholera, conjunctivitis, cystitis, diphtheria, bacterial endocarditis, epiglottitis, gangerene, gastroenteritis, glanders, gonorrhea, Legionnaire's disease, leptospirosis, bacterial meningitis, plague, bacterial pneumonia, otitis media, puerperal sepsis, pyronephritis, rheumatic fever, Rocky Mountain spotted fever, scarlet fever, sinusitis, streptococcal pharyngitis, syphilis, tetanus, toxic shock syndrome, tuberculosis, tularemia, typhoid fever, typhus, pertussis and etc….

The instant specification provides assays to test compounds of the formula (about 20 compounds) in vitro and/or in vivo and discloses that said compound exhibit bacillus, brucella, caulobacter growth inhibiting activity. However, there is no demonstrated correlation that the tests and results apply to all of the diseases or disorders embraced by the instant claims.

In view of limited numbers of working examples, the insufficient amount of guidance present in the specification, the nature of the invention, the state of art, the

breadth of the claim and the relative skills of the artisan and the predictability of the pharmaceutical art where many specific differences or different physicochemical properties are existed among unrelated structural compounds would take "undue painstaking experimentation" to practice the invention commensurate in scope with these claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 52-61 are rejected under 35 U.S.C. 102(e) as being anticipated by Lee et al. (US 20050054644) or Benkovic et al. (US 20040259833). This rejection is analogous to the previous rejection mailed 07/31/2008. This rejection is maintained because the applicant has not effective perfected priority claim during the time period set forth in 37 CFR 1.78(a) as discussed above.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the

reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The '644 or '833 PG-pub discloses a method of treating bacteria e.g., Helicobacter as the instant method utilizing the same boron containing compounds. The claimed inhibition of DNA methyltransferase is a property inherent to the compound used in the method, (see the '644 published application).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 52-61 are, as amended, are rejected under 35 U.S.C. 103(a) as being unpatentable Patel et al (5348947) in view of Vermeulen et al (5872104) and Barney et al (6068973)and Lonetto et al (6165762). This rejection is analogous to the previous rejection mailed 07/31/2008. This rejection is maintained because the applicant has not

effective perfected priority claim during the time period set forth in 37 CFR 1.78(a) as discussed above.

Patel discloses throughout the patent at e.g., the claims a method of treating fungus by administering a diarylboron ester and thioester having the formula as shown at e.g., the abstract. Patel does not disclose that said diarylboron ester can treat a DNA methyltransferase mediated bacteria induced disease.

Vermeulen discloses throughout the patent at e.g., col. 3, lines 4-64:
A method comprising administering to an animal (including a human patient) that has, or is suspected to have a microbial or bacterial infection, a therapeutically effective amount of pharmacologically acceptable antimicrobial agent formulation in combination with a therapeutic amount of a pharmacologically acceptable formulation of a second agent effective to inhibit methylation, e.g., effective to inhibit RNA methylation. The invention may thus be employed to treat both systemic and localized microbial and bacterial infections by introducing the combination of agents into the general circulation or by applying the combination, e.g., topically to a specific site, such as a wound or burn, or to the eye, ear or other site of infection.

The "second agents" for use in the invention are generally methylation inhibitors, and are also referred to herein as "inhibitors" and "modifiers" The second agent inhibitors should be used in amounts effective to inhibit methylation in a microorganism or bacterium, as exemplified by an amount effective to inhibit RNA methylation, synthesis and/or maturation in an MLS-susceptible bacterium. Suitable amounts effective to inhibit methylation will be known, or readily identifiable, to those of skill in the art. Effective inhibitory amounts are the amounts that have previously been shown in the scientific

literature to inhibit methylation generally or to inhibit a specific methylation step. In addition to the present disclosure and the references specifically incorporated herein, there is considerable scientific literature concerning methylation inhibitors that may be utilized in light of the inventors' discovery that such compounds may be effectively combined with antibiotics and other antimicrobial agents. Amounts effective to inhibit methylation may also be measured, rather than identified from the published literature. Most simply, this is achieved by determining the amount effective to increase microbial or bacterial killing when used in combination with an antimicrobial agent, i.e., by determining an amount effective to reduce antimicrobial resistance. The determinations of effective inhibitory amounts and therapeutic doses will be routine to those of skill in the art given the teachings of the present disclosure, including the detailed methodology and the effective amounts of various agents disclosed, e.g., in Table 8 and throughout the detailed examples.

Patel does not disclose bacteria. However, Vermeulen discloses in general bacteria and microbes.

Barney et al throughout the patent discloses the different bacterial species such as Agrobacterium, Rhizobium and Helicobacter. Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to treat bacteria or other microbes such as fungi in the method of Patel in view of Vermuelen's disclosure that not only bacteria are treated by inhibitors of DNA methylase but other microbes as well. One having ordinary skill in the art would know that a fungus is one type of microorganism(s) as taught by Vermuelen. Vermeulen teaches treatment of bacteria in general and does not seem to limit to those disclosed therein. It would be within the

ordinary skill in the art at the time the invention was made to choose the specific bacteria depending upon the bacteria desired to be treated. The bacteria Agrobacterium, Rhizobium and Helicobacter are known to have been treated in the art whether via the mechanism of DNA methyltransferase inhibition or by other mechanistic pathway as evidenced by Lonetto et al, which discloses at e.g., col. 19, lines 50-67:

Helicobacter pylori (herein H. pylori) bacteria infect the stomachs of over one-third of the world's population causing stomach cancer, ulcers, and gastritis (International Agency for Research on Cancer (1994) Schistosomes, Liver Flukes and Heiicobacter Pylori ..... Moreover, the international Agency for Research on Cancer recently recognized a cause-and-effect relationship between H. pylori and gastric adenocarcinoma, classifying the bacterium as a Group I (definite) carcinogen. Preferred antimicrobial compounds of the invention (agonists and antagonists of apt) found using screens provided by the invention, particularly broad- spectrum antibiotics, should be useful in the treatment of H. pylori infection. Such treatment should decrease the advent of H. pylori-induced cancers, such as gastrointestinal carcinoma.

Double Patenting Rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the

reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 52-61, as amended, are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 19-23 of US Patent No. 7465836 (which is corresponds to US application No. 10/868268).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the instant invention overlaps with the patented claims. Both of the instant claims and those of the cited patent are drawn to administration of the same or similar compounds represented by the formula for treatment of DNA methyltransferase mediated bacterium induced disease.

Conclusion

10. No Claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

/Brian-Yong S Kwon/
Primary Examiner, Art Unit 1614